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Katzka, David A ; Fox, Mark

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Achalasia: When a simple disease becomes complex

David A. Katzka MD, Mark Fox MD MA

Author affiliations:

[1] Division of Gastroenterology and Hepatology, Mayo 9, Mayo Clinic, 200 First Ave., S.W. Rochester, MN 55905, USA

[2] Division of Gastroenterology and Hepatology, University Hospital Zürich, Zürich, Switzerland.

[3] Digestive Function: Basel, Laboratory and Clinic for motility disorders and functional Gastrointestinal diseases, Centre for integrative Gastroenterology, Klinik Arlesheim, Arlesheim, Switzerland.

Corresponding author:

Prof. Dr. Mark Fox

Digestive Function: Basel, Laboratory and Clinic for Motility Disorders and Functional GI Diseases, Klinik Arlesheim, Arlesheim, Switzerland

Email: dr.mark.fox@gmail.com

Tel: +41 79 1934795

Editorial

Textbooks present achalasia as a relatively simple disease defined by esophageal aperistalsis and impaired "relaxation pressure" of the EGJ with radiographic findings that typically accompany these manometric findings. The etiology of this disorder is not known but cases have been linked to an autoimmune process limited to the myenteric plexus of the lower esophageal sphincter (LES) and initiated by molecular mimicry of a viral epitope, such as HSV.[1, 2] Recent recognition that certain types of achalasia have esophageal spasm or even preserved peristalsis (EGJ outlet obstruction) has broadened the definition of the disease.[3, 4] At the same time the wide spectrum of histopathologic findings - from complete neuronal loss to lymphocytic inflammation to apparently normal histopathology - emphasizes that "achalasia" is a heterogeneous condition.[3, 5] There are also a plethora of secondary causes, including genetic conditions, paraneoplastic syndromes,[6] Chagas Disease[7] and opioid induced esophageal dysmotility.[8] Additionally, both benign inflammatory and malignant processes that involve the EGJ may produce findings similar to achalasia. Achalasia can be viewed as one disease with multiple potential etiologies, with the commonality being EGJ outlet obstruction.

The EGJ has a complex functional anatomy that includes an intrinsic physiological sphincter of smooth-muscle within the abdominal oesophagus [LES] and gastric cardia (clasp and sling fibers) together with an extrinsic crural diaphragm (CD) of skeletal muscle (Figure HV panel).[9] Previously the focus of attention in achalasia has been almost entirely on impaired LES function, although impaired relaxation of the proximal stomach has been documented.[10, 11]

In this edition of *Gastroenterology,* researchers led by Ravi Mittal combined 3-dimensional high-resolution manometry (3D-HRM) with detailed analysis of computed tomography images to study the esophago-gastric junction (EGJ) in patients with achalasia and healthy controls.(Mittal reference) This novel contribution describes possible abnormalities of the esophageal hiatus and CD muscle in idiopathic achalasia.(Mittal reference) Consistent with previous reports,[12] the authors demonstrated an asymmetric, extrinsic CD component to EGJ pressure superimposed on the intrinsic LES. In all subjects, the LES length was greater on the lesser curvature as compared to the greater curvature of the stomach; whereas, LES related pressures were greater towards the greater curvature, at the esophago-gastric insertion angle - termed angle of His in anatomic studies (Figure HV panel). In achalasia patients the LES pressure distribution and the location of CD contraction within the EGJ high pressure zone were more variable and, in many cases, appeared to be abnormal. The authors attributed these changes to the asymmetric pull of the "noose-shaped" right crura on the abdominal esophagus.

Although innovative, the measurements derived from this methodology have not been validated and the soft-tissue resolution of CT to differentiate EGJ structures is at the limit of what is possible even with Magnetic Resonance (MR) Imaging.[13] Further, the mechanistic inferences are speculative and not necessarily consistent with published literature or clinical experience. Far from the LES being "tightly anchored" to the hiatus, striking shortening of the esophagus with pan-esophageal pressurization mediated by longitudinal muscle contraction is observed in achalasia patients and, when this occurs, the LES can be drawn into the chest while the diaphragmatic pinch remains in position![14, 15] Further,

surgeons do not report that the LES is neither firmly attached to the CD nor trapped within the hiatus in patients referred for Heller Myotomy (personal communication, Prof. Robert Rosenberg). However, repeated "pulling" on the phreno-esophageal ligaments during esophageal shortening could explain the physical breaks (muscle tears?) in the left crus of the diaphragm observed in the paper.

It is also clear that observational data cannot distinguish cause from effect. Choosing appropriate interventions to test the hypothesis is a challenge; however, Brasseur et al. have shown that it can be done by "pharmacological dissection".[9] Mittal et al. refer to a case in which injection of botulinum toxin into the sphincter region inadvertently paralyzed the CD and obliterated the esophago-gastric insertion angle. As botulinum toxin produces profound relaxation in both smooth and striated muscle, the effects of injection into the LES, gastric cardia or CD could produce the same result and, therefore, cannot be used to differentiate biophysical effects of these structures. Studies that combined MR imaging and HRM to assess EGJ structure and function in gastro-esophageal reflux disease (GERD) may provide more insight.[16, 17] The angle of His is more obtuse in GERD patients in healthy controls,[17] which is interesting to contrast with the acute insertion angle seen in achalasia patients (Figure Achalasia and GERD panel). This observation could be explained by a wide hiatus or weak CD function, both common in GERD patients; however, anatomical studies indicate that the clasp and sling fibers at the gastric cardia also maintain the angle of His. The biophysical mechanism of the EGJ reflux barrier was investigated by repeating measurements after treatment with baclofen. This GABA-B agonist not only restored the insertion angle in GERD patients but also reduced transient LES relaxations and reflux events.[16] Baclofen increases tone in the LES and the clasp and sling muscle fibers via effects on the vagal nerve;[18] however, it relaxes the crural diaphragm... an effect that explains its utility in hiccups![19] Together, the results support the hypothesis that the acute insertion angle in achalasia and the obtuse insertion angle in GERD patients are related to variation in muscle tone within the clasp and sling fibers of the proximal stomach and not, or not only, with abnormal hiatal anatomy or CD function (Figure).

Another issue is the part of the hypothesis that suggests that degenerative changes in the spine can impact on CD function is unlikely to apply in younger patients with achalasia. Although previous work has demonstrated neurodegeneration secondary to obstruction in an animal model of achalasia, this etiology is hard to reconcile with evidence of autoimmune etiology in many patients.[2, 5]

Achalasia may once have appeared to be a simple motility disorder; however, it is now clear that many etiologies result in a common presentation that responds to treatment that relieves EGJ outlet obstruction. It is hoped that improved understanding of the disease will lead to individual treatment directed at the underlying pathophysiology. With researchers such as Mittal et al. prepared to develop innovative methods and present novel findings, this goal is getting closer.

Figure Legend

Schematic diagram of esophago-gastric junction (EGJ) anatomy in health (central panel). Immediately below the lower esophageal sphincter, clasp and sling fibres fanning out from the greater to the lesser curvature form the distal component of the esophago-gastric junction high pressure zone. Increased density of these fibers on the greater than the lesser curvature could explain the variation in length and pressure of the sphincter between these two positions observed on 3D-HRM (lower panel). This anatomical arrangement may also maintain the esophago-gastic insertion angle. In achalasia patients with high tone in both components of the intrinsic sphincter the pressure is abnormally high and the insertion angle is acute (left panel). In GERD patients with low tone in the intrinsic sphincter the pressure is low and the angle is obtuse (right panel); however, administration of the GABA-B agonist baclofen increases pressure and restores the angle towards normal values. An alternative hypothesis proposed by Mittal et al. in this edition of Gastoenterology states that the changes in the structure and function of the crural diaphragm produces the effects seen on 3D-HRM and variation in the esophago-gastic insertion angle in health and disease.

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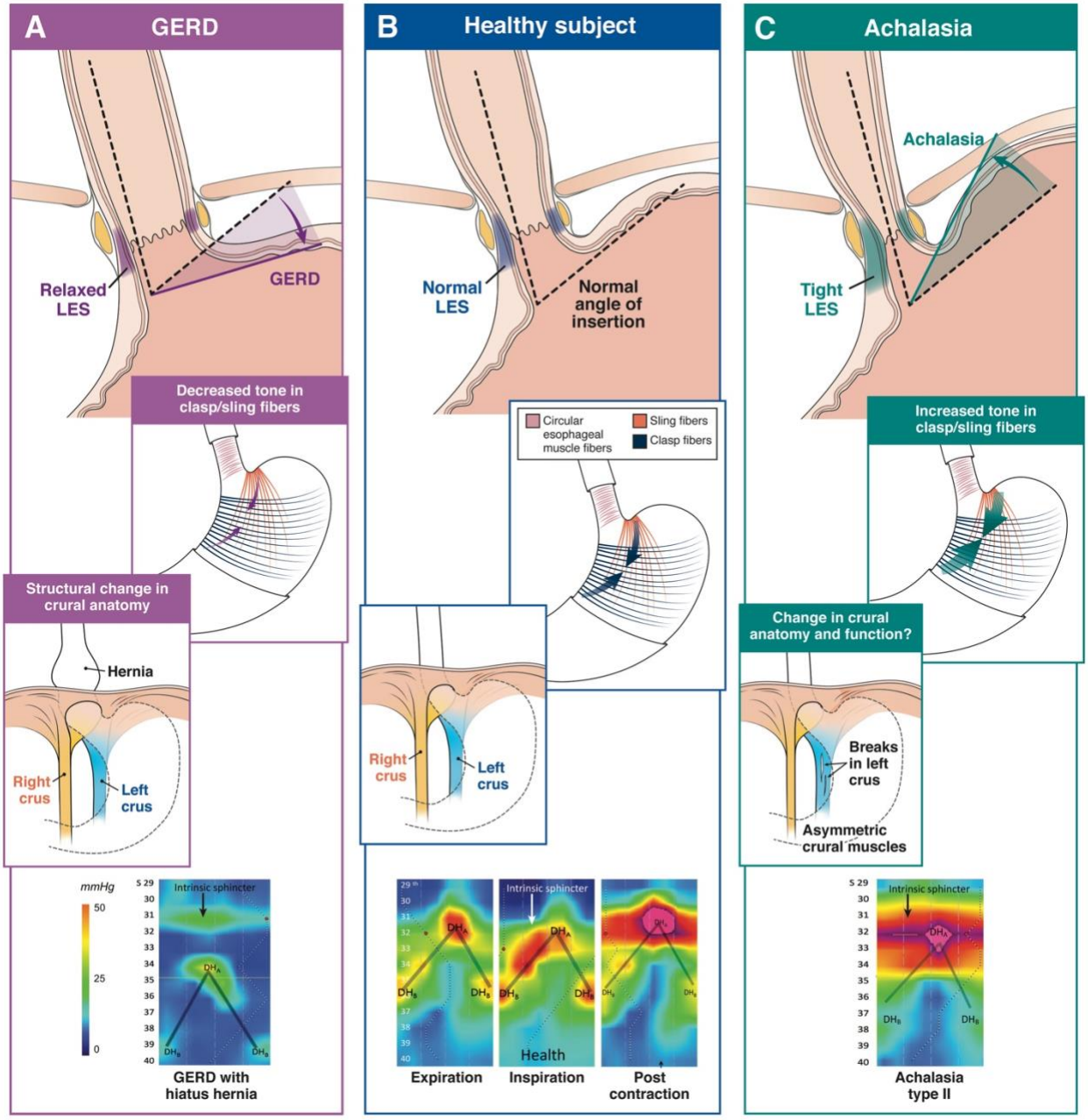
A
GERD
Relaxed LES
GERD
Decreased tone in clasp/sling fibers
Structural change in crural anatomy
Hernia
Right crus
Left crus
mmHg
50
25
0
Intrinsic sphincter
GERD with hiatus hernia
B
Healthy subject
Normal LES
Normal angle of insertion
Circular esophageal muscle fibers
Sling fibers
Clasp fibers
Right crus
Left crus
Intrinsic sphincter
Health
Expiration
Inspiration
Post contraction
C
Achalasia
Achalasia
Tight LES
Increased tone in clasp/sling fibers
Change in crural anatomy and function?
Breaks in left crus
Asymmetric crural muscles
Intrinsic sphincter
Achalasia type II